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TITLE: A Population-Based Randomized Trial to Assess the Effects of Short-Term Cessation of HRT on Mammography Assessments and Breast Density

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14. ABSTRACT

This randomized controlled trial is designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We are projecting we will recruit about 1,500 women who will be randomized to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer-assisted method and mammography recall rates from an expert radiologist review of the mammograms; both readers will be blinded to HRT status. We started recruiting women 11/2004; through 5/2006, we have contacted 3,205 potentially eligible women. Among women contacted, 33% have agreed, 40% have refused and 28% have been ineligible. Among women who have agreed to participate, 25% have withdrawn from the study. The HSRRB reviewed and approved several modifications to study materials during 2004-5. We submitted additional changes to our materials to increase recruitment in June 2005, which the HSRRB approved in September 2005.

15. SUBJECT TERMS
Randomized controlled trial, Mammography, Health care setting, hormone replacement therapy, Breast Density

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INTRODUCTION:

This randomized controlled trial is designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We are using automated to identify HRT users who are due for screening mammograms. Women are being recruited through mailed correspondence and telephone contact. We are projecting to recruit about 1,500 women to randomize to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer-assisted method. Mammography recall rates are being determined from an expert radiologist review of the mammograms. Both readers are blinded to HRT status. We will test whether: 1) HRT cessation 1 or 2 months before a screening mammogram reduces the likelihood of receiving a recommendation for additional evaluation (recall) compared to women who continue using HRT; 2) HRT cessation for 1 versus 2 months affects the likelihood of receiving a recommendation for additional evaluation; and 3) there is a greater change in breast density (to lower breast density) among women who stop HRT 1 or 2 months before a screening mammogram to those who do not stop HRT. Change in breast density will be measured as the difference between breast density on the screening mammogram before the trial (while on HRT) and on the mammogram during the trial. As part of this trial we will also evaluate: 1) women's tolerance (defined as continued cessation) for short-term (1-2 months) HRT cessation, 2) the rate of HRT re-initiation after participation in the trial, and 3) rates of reported adverse events (return of hot flashes, thromboembolic events within the first 6-months after re-initiation, and return of bleeding with re-initiation among previously amenorrheic women) across randomization groups.

BODY:

Progress on the scope of work (SOW) outlined in the original proposal.

Task A. Recruit 1500 women to participate in the trial

Study recruitment began in November 2004, after final HSRRB approval. In the ensuing 19 months we have contacted 3,205 women, an average of 169 per month.

Current Recruitment (5/26/2006):

Selected	3436		
Contacted	3205	93.3%	% of selected
Ineligible	891	27.8%	% of contacted
Eligible	2314	72.2%	% of contacted
Refused	1268	54.8%	% of eligible
Agreed	1046	45.2%	% of eligible
Withdrew before consent	*195*	*18.6%*	*% of agreed*
Withdrew after consent	*64*	*6.1%*	*% of agreed*
Total withdrew after recruited	259	24.8%	% of agreed
Study participants	787	24.6%	% of contacted

In our original proposal, we estimated an enrollment of 21.9% of the women approached. We are above target by recruiting 24.6% of women approached. However, the pool of potentially eligible women declined in the wake of the report of adverse effects of hormone therapy from the Women's Health Initiative in July 2002. HRT use has decreased among members of GHC to less than 30% of the levels in 2001 and the number of potentially eligible women has slowly dropped each month. We are approaching all potentially eligible women.

With the award of the supplemental funds, we will extend recruiting for 15 months beyond the previous end date for recruiting of 5/31/2006 to 8/31/07 and expect to add the additional 713 subjects needed to meet the recruiting goal.

Task B. Develop Study Materials

The study staff developed study materials and received approval for all materials from the GHC HSRC and the HSRRB. Staff met with the Advisory board members once during the last year and has communicated via email.

Task C. Monitor the safety of HRT cessation and initiation

The Study Nurse has collected information on any adverse event identified from self-report, toll free phone number, or automated administrative data. The Nurse has followed all procedures for reporting Adverse Events to GHC HSRC and DOD HSRRB. The programmer has reviewed automated administrative data each month to extract information on women enrolled in the study to identify adverse events noted in in-patient and out-patient procedures using ICD-9 and CPT codes. The study physician has reviewed all adverse events identified from self-report, toll free phone number, or automated administrative data for relationship to study participation. The study biostatistician has generated and distributed one Data Safety and Monitoring Board report to the DSMB. The Data Safety Monitoring Board met once during this period to review study progress and safety. The DSMB will meet again on June 27, 2006.

Task D. Ascertain outcomes from mammograms (mammographic density and clinical interpretation)

The first reviews of mammograms for density and clinical assessment were completed in June 2005. Since then the study radiologist has assessed 577 mammograms of the 586 clinical mammograms on study participants available (98%) and the Research Specialist has entered information from the radiology assessment form into the mammogram database. The Research Specialist has also digitally scanned each study subject's mammograms for density determination. Monitoring GHC automated pharmacy data for reinitiation of HRT is ongoing. 621 women have returned a follow-up questionnaire that includes questions on their intention for restarting HRT and compliance with HRT cessation during the study. The questionnaire is mailed to women two weeks prior to their mammogram appointment.

Task E. Data quality and control

Questionnaires are scanned weekly using Teleform technology that has built-in logic checks for the data. The radiologist fills out the Radiology Assessment form for each subject after completing reading the mammograms and the Research Specialist enters the form data into the mammogram database. The study programmer runs quality checks on those data monthly. The quality control digital images are being randomly selected, rescanned and re-read for density outcomes on an ongoing basis.

Task F. Final analyses and report writing

Task F is not complete; both elements require data collection to be completed; however, we did present preliminary data about the study at the DoD's Era of Hope meeting in June 2005 (see reference section below).

KEY RESEARCH ACCOMPLISHMENTS:

Between June 1, 2005 and May 31, 2006, we have:

- Continued recruitment
- Refined tracking and reporting procedures
- Met with Advisory Committee
- Received approval on IRB modifications from GHC HSRC and from HSRRB.

Date	*Submitted to*	*Received from*	*Content of submission*
6/2/04	GHC		Modification request to make changes to materials in an attempt to increase participation rates: • Invitation letter

Date	Submitted to	Received from	Content of submission
			• Survey script • Study brochure • Sending 2nd consent form to non-responders • Sending 2nd set of questionnaires to non-responders • Call women who have not returned consent • Call women to complete baseline or follow-up questionnaire via telephone if have not responded to 2 mailings • Changes to protocol that result from the suggested changes described above
6/24/05		GHC	Approval of modification submitted 6/2/2004 Stamped copy of consent form with expiration of 10/18/2005 Stamped copy of protocol with expiration of 10/18/2005
6/29/05	HSRRB		Submission of modification #3 approved by GHC 6/24/05 included: • Cover memo • Packet submitted to GHC IRB 6/2/05 • GHC IRB response with documented approval dated 6/24/05 • Clean copy of consent and protocol with stamped date of expiration (10/18/05)
7/21/05	GHC		Request approval to change contact number on the study brochure to the READ hotline rather than CHS Survey. This request was made in response to concerns raised by DOD.
7/21/05	HSRRB Via e-mail from Diana Buist.		Division of modification #3 into two parts. One for expedited review and the other for full review. Expedited: • Protocol (attachment 1A) - changed to include the procedures for the materials listed below □ Cover letter for mailing second set of consent forms (Attachment 4) □ Cover letter for mailing second set of questionnaires (Attachment 5) □ Contact script for reminding participant to return consent forms (Attachment 6) □ Contact script for completing baseline questionnaire by telephone (Attachment 7) □ Contact script for completing follow up questionnaire by telephone (Attachment 8) □ Consent Form (Attachment 9) change in study personnel Full review: • Letter to participants informing them of the study and inviting participation (Attachment 1B) □ Revision to eligibility screening script addressing women's concerns about stopping HRT (Attachment 2) □ Revision to study brochure to more accurately inform women what the study is about, what is being studied and how they may benefit. (Attachment 3 – we have included the revised brochure and the original brochure; both are labeled attachment 3 and indicate if it is the revised or original brochure)
7/25/05		GHC	Approval of modification to brochure contact number
8/1/05		HSRRB	Approval for expedited review items listed above
8/24/05		HSRRB	Verbal approval for full review items listed above

Date	Submitted to	Received from	Content of submission
8/31/05	GHC		Annual continuation review
9/20/05		GHC	Continuation review Approval; Request for clarification of procedure for reporting Adverse Events
9/29/05		HSRRB	Approval for full review of protocol amendments listed above
10/10/05	GHC		Response from continuation review; Protocol Modification to clarify Adverse Event Reporting and Adverse Event Report Form
10/18/05		GHC	Approval of modifications to protocol and AE Report form
10/25/05	HSRRB		GHC approval for annual Continuation Review Report and response with modifications approved
10/27/05		HSRRB	Approval for GHC Continuation Review Report and modifications
11/8/05	GHC		Notification of Serious Adverse Event: death of a participant not due to study participation (motorcycle accident)
11/9/05	HSRRB		Notification of Serious Adverse Event: death of a subject unrelated to participation in study (motorcycle accident)
11/15/05		GHC	Serious Adverse Event report reviewed by GHC HSRC
5/8/2006	GHC		Report of Unanticipated Problem: theft of mammography films from Central Radiology Clinic
5/31/06	HSRRB		Report of Unanticipated Problem: theft of mammography films from Central Radiology Clinic

REPORTABLE OUTCOMES:

Recruitment of study subjects began in November 2004. To date, we have no reportable outcomes.

CONCLUSIONS:

We are experiencing a higher proportion of refusals and withdrawal after agreeing to participate in the trial than is typical for GHC studies. In 2004, we spent considerable time talking with our survey department to determine ways we could improve the recruitment materials to address the concerns and/or questions of women who are refusing; we recently completed another review of materials and procedures. We made modifications to our recruitment materials that address these issues brought up by the survey department: 1) how will participation directly influence women, and 2) what if women cannot comply with staying off their hormones if they are randomized to one of the 2 cessation arms that were reviewed and approved by our local IRB (June 2005) and the HSRRB (September 2005).

One of our key findings to date is that the cohort of women who are still using HRT following the results of the Women's Health Initiative (WHI) may be substantially different than women who were using before WHI. As such, understanding whether this intervention would be acceptable to women still using HRT is likely to become a major focus of this study. For example, if we find that women who stop using hormones have a significant reduction in breast density and/or recall rates, it may be that the intervention is still unacceptable to the majority of women who are still using HRT. We are collecting information on compliance, reinitiation and symptoms, so we will be well positioned to address acceptability of the intervention.

REFERENCES:

Buist DSM, Newton KM, Reed S, Anderson ML, Aiello EA, King E, Palmer L, Seger, D. Can Short-Term Hormone Therapy Cessation Before Mammography Decrease Breast Density And Improve Mammography Performance? A Randomized Trial. Department of Defense's Era of Hope. June 8-11, 2005. Philadelphia, PA.